Case Report

An Unusual Presentation of Low Grade Central Osteosarcoma in the Distal Femur of a Sixty-eight Year Old Male Mimicking Fibrocartilaginous Mesenchymoma

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Low grade central osteosarcoma is a rare intramedullary bone tumor that presents a diagnostic challenge due to its radiographic and histologic overlap with other low grade intraosseous lesions. Here we report a case of a 68 year old male presenting with local pain in the right distal thigh. An MRI study showed a 4.8 cm lesion in the metadiaphysis of the distal femur with extension into the cortex and aggressive periosteal reaction. Multiple biopsies were performed in an attempt to reach a conclusive diagnosis: 1) A CT guided FNA and biopsy revealed a low nuclear grade spindle cell neoplasm with new bone formation; 2) Subsequent core biopsy showed bland cartilage with no atypical features and reactive new bone formation; 3) An excisional biopsy was reported as a matrix (hyaline cartilage and bone) producing neoplasm showing features most consistent with fibrocartilaginous mesenchymoma. Due to uncertain malignant potential, the patient underwent complete resection of the distal femur with the final diagnosis of low grade central osteosarcoma. Molecular studies performed showed lack of CPM amplification. This case report illustrates the diagnostic challenge of an atypical case of low grade central osteosarcoma. It required multiple procedures, molecular studies, and correlating the histology to the radiology and clinical picture to arrive at the correct diagnosis.

[N A J Med Sci. 2016;9(2):78-82. DOI: 10.7156/najms.2016.0902078]

Key Words: *Aneurysmal bone cyst (ABC), dedifferentiated chondrosarcoma (DDCS), fibrocartilaginous mesenchymoma (FCM), fibrous dysplasia (FD), fibrocartilaginous dysplasia (FCD), low grade central osteosarcoma (LGCO)*

INTRODUCTION

Low grade central osteosarcoma (LGCO) is a rare well-differentiated subtype of osteosarcoma that accounts for approximately 1-2% of all osteosarcomas.[1,2] With a roughly equal male to female ratio, the majority of cases occur in the third decade of life. The most common clinical manifestation is long-standing pain while less frequent complaints include a palpable mass, swelling, and pathological fractures. The lesion is centrally located in the intramedullary space and most commonly involves the metaphysis or diametaphysis of the distal femur or proximal tibia with epiphyseal involvement by large sized lesions.[1,2]

The radiologic features of LGCO are variable but generally show a mixed lytic and fibro-osseous lesion with cortical erosion and soft tissue extension.[3] Grossly, LGCOs are often large tumors with variable mineralization and white rubbery to gritty cut surface. Histologically, the tumor is composed of interlacing fascicles of spindle cells with mild atypia and occasional mitotic figures infiltrating between bone trabeculae.[2,4,5] Surgical excision with wide (negative) margins results in a generally good prognosis and 5 and 10 year survival rates reported to be greater than 90% and 80%, respectively.[2] Local recurrence and distal metastasis are very rare. The most common differential diagnosis of LGCO includes fibrous dysplasia (FD), fibrocartilaginous dysplasia (FCD), and fibrocartilaginous mesenchymoma (FCM).

Fibrocartilaginous mesenchymoma (FCM) is an extremely rare primary bone tumor with only 23 cases of reported in the literature since its first inception in 1984.[6-9] Often considered on a spectrum with FCD and FD, the majority of FCM cases occur in the long bones of individuals in their second decade of life.[10-12] Patients commonly complain of mild pain, discomfort, redness, and local tenderness.[11] Radiologically, FCM presents as an expansile, locally aggressive radiolucent lesion with punctate calcifications and cortical destruction often with extension into the soft tissue.[7,9,11,12] Histology of these tumors show a variably cellular fibroblastic proliferation without significant cytological atypia or mitoses, a characteristic cartilaginous component resembling epiphyseal growth plate, and endochondral bone formation.[7,11-13] Local relapses have occurred secondary to incomplete tumor removal but no distant metastases or death

Received 12/06/2015; Revised 04/01/2016; Accepted 04/05/2015
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has been reported. Due to local destructive behavior and risk of recurrence, the most effective treatment is complete surgical excision.

Low grade intraosseous neoplasms are a challenging diagnostic category. The clinical demographics and symptoms are often similar. There is significant overlap in their radiologic and histologic features. Consequently, multiple biopsies and ultimately a resection specimen may be necessary before a correct final diagnosis is reached.
Ancillary testing with immunohistochemistry and molecular tests targeting cyclin-dependent kinase 4 (CDK4) and murine double-minute type 2 (MDM2) have proven useful in delineating LGCO from benign fibro-osseous lesions with positive staining being sensitive for LGCO.[12,14,15] CPM and CDK4 are genes on chromosome 12q that are consistently co-amplified with MDM2. Several tumors can harbor CPM, CDK4, and MDM2 amplification: subtypes of sarcoma (including LGCO), leukemia, lymphoma, and carcinoma.[14-17] Reported specificities for LGCO have been variable and a negative staining pattern does not rule out the diagnosis.[14,15] Correlating the clinical, radiologic, histologic, and molecular findings are integral for the accurate evaluation of these lesions.

Here we report a challenging case of a low grade intramedullary bone neoplasm with multiple biopsies showing different histologic features and a molecular study showing a lack of CPM amplification. The final resection specimen diagnosis was LGCO.

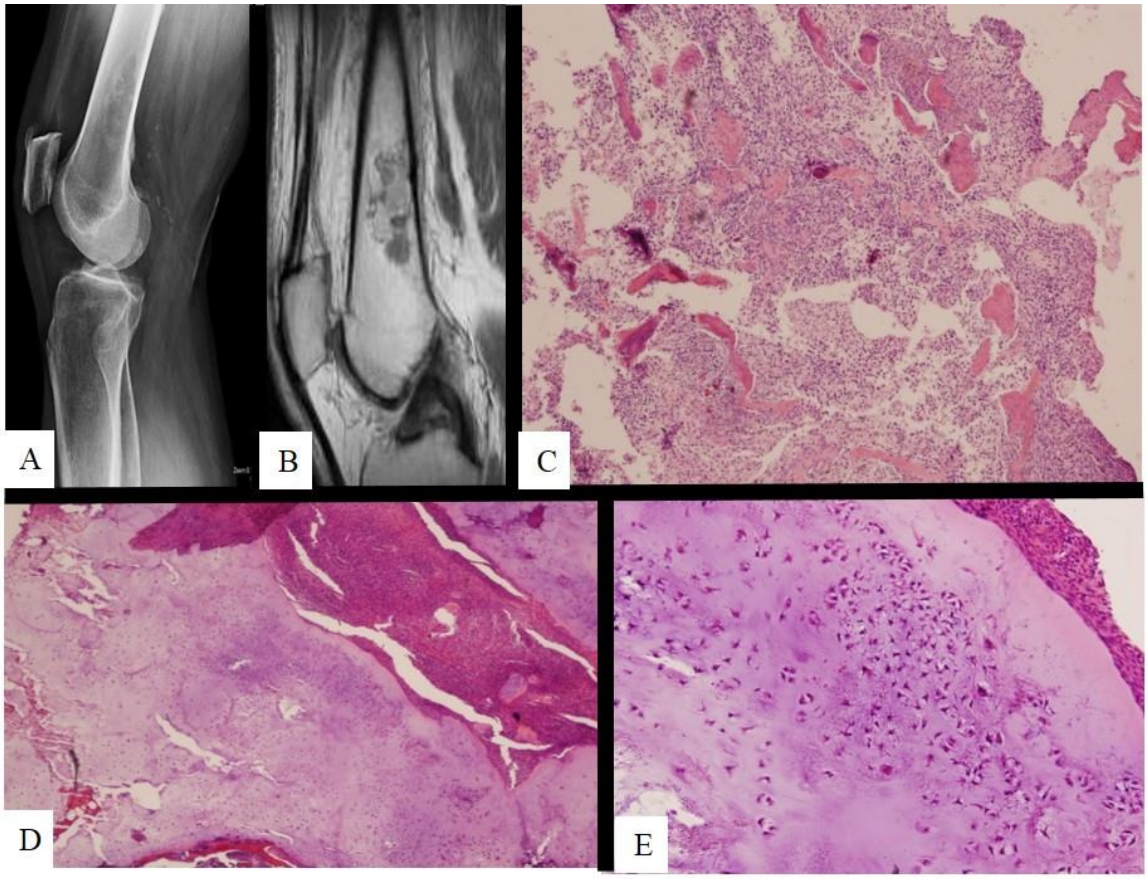

Figure 1. Radiology and histopathology images of excisional biopsy of tumor: **A)** X-ray of distal femur. **B)** MRI of the tumor. **C)** Hypercellular spindle cell component with atypia (H&E, 40x). **D)** Spindle cell lesion with cartilage component (H&E, 100x). **E)** High power view of the atypical cartilage (H&E, 200x).

CASE PRESENTATION

A 68-year-old Caucasian male presented with pain in the right distal thigh while driving. Physical examination revealed a non-tender, stable knee joint with no effusion and full range of motion. An X-ray study showed a radiolucent lesion in the distal femur with foci of increased density representing either chondroid or osteoid matrix **(Figure 1A)**.

A subsequent MRI study showed an aggressive marrow lesion within the medial aspect of the distal femoral metadiaphysis measuring 4.8 x 2.7 x 2.3 cm **(Figure 1B)**. The lesion had a low T1 signal and heterogeneously increased T2 signal. It was associated with adjacent marrow edema and extended into the cortex with prominent endosteal

scalloping. An aggressive periosteal reaction with thickening and pericortical edema were present. The differential diagnosis based on radiology included metastatic disease, multiple myeloma, lymphoma, osteosarcoma, chondrosarcoma, and malignant fibrous histiocytoma.

A CT guided FNA and tissue biopsy was subsequently performed. The biopsy specimen was non-diagnostic showing scant fragments of bone with focal new bone formation. The cytologic specimen revealed a low nuclear grade spindle cell neoplasm with new bone formation. Immunohistochemistry was performed on the cytology cell block. The lesional spindle cells were positive for vimentin; they were negative for CK7, CK20, and CD31. At that time, the differential diagnosis included fibro-osseous lesions and low nuclear grade neoplasms.

A core biopsy was performed in an attempt to reach a more conclusive diagnosis. Histology showed fragments of bland cartilage composed of single, benign appearing cells within single lacunae. No areas of increased cellularity, binucleation, or nuclear atypia were identified. Focal calcification and ossification were noted. Reactive new bone formation with vascularization was present with no evidence of a destructive growth pattern. The histologic features were compatible with enchondroma associated with reactive new bone formation, but radiologic features were discordant. The case was sent out for external consultation. The final diagnosis was still descriptive and inconclusive ("bland cartilage and reactive new bone formation").

Subsequently, the patient elected to proceed with curettage and cementation. Histological sections of the specimen obtained showed neoplastic cartilage, bone and spindle cells (**Figure 1C-1E**). The hyaline cartilage component had focal areas of increased cellularity but lacked features of obvious malignancy and the bone is unremarkable. The spindle cells demonstrated mild to focally moderate cytological atypia, increased mitoses, and variable chondroid and osteoid production. The differential possibilities of FD, LGCO, FCM, dedifferentiated chondrosarcoma (DDCS), and integrating the radiographic findings were done. The final diagnosis was reported via outside consultation (orthopedic pathologist) as "a matrix (hyaline cartilage and bone) producing neoplasm showing features most consistent with FCM".

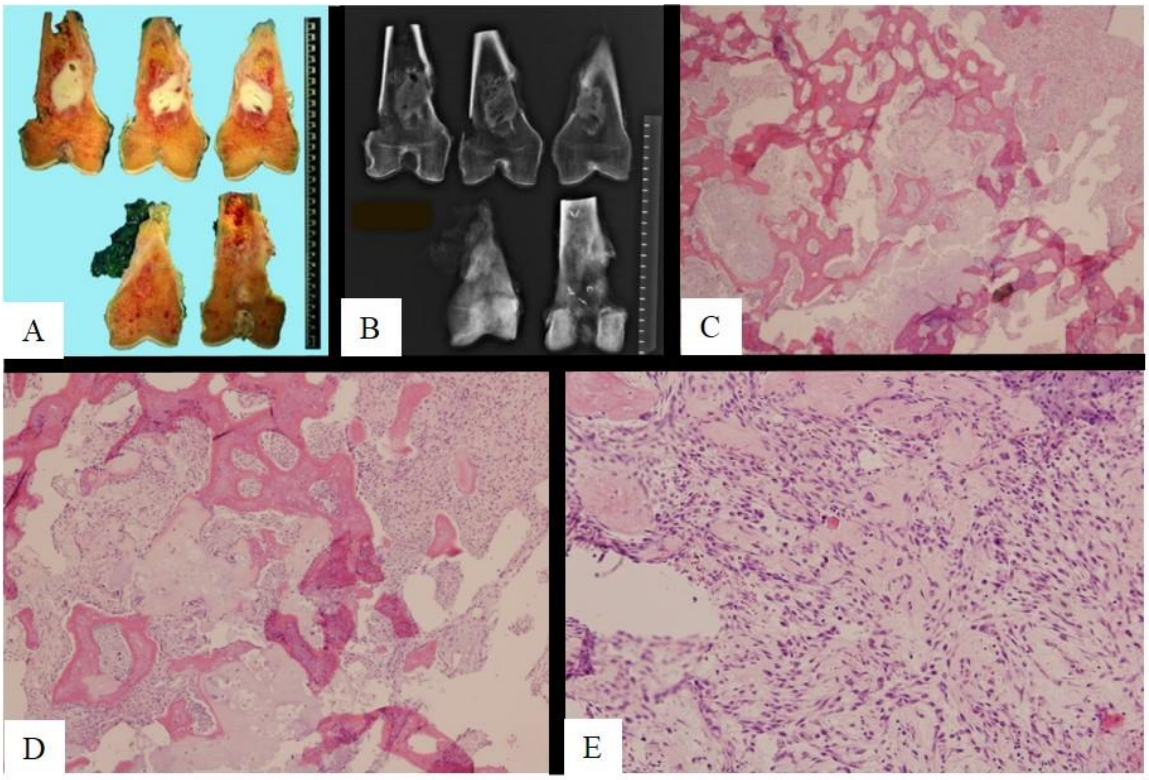

Figure 2. Resection of right distal femur: **A)** Gross picture of serially sectioned distal femur after the previous. curettage biopsy filled with cement. **B)** Corresponding X-ray of the sections. **C)** Low power view of the tumor (H&E, 40x). **D)** Cartilage component in the tumor (H&E,100x). **E)** Hypercellular spindle cell component with atypia and mitosis (H&E, 200x).

The lesion was clinically considered to have uncertain malignant potential because of radiologic features of malignancy. Consequently, the patient underwent resection of the distal femur **(Figure 2 A-E)**. Grossly, the resection revealed an approximately 7 x 4 x 3 cm tan, hemorrhagic, firm and irregular tumor with 4 cm of cement in the center.

Histologically, the specimen showed spindle cells with focal mild to moderate cytologic atypia, variable osteoid production, and readily identifiable mitotic figures. Areas of cortical destruction and soft tissue extension were present. The neoplastic cartilage, as seen in the excisional biopsy, was notably absent. No histologic evidence of a high-grade component (dedifferentiation) was seen. Reevaluation of the case via outside consultation (orthopedic pathologist), coupled by the radiologic findings and histologic features resulted in a final diagnosis of LGCO. Molecular studies for CPM amplification by in situ hybridization showed no amplification.

Table 1. Differential diagnosis of LGCO.

	LGCO	FD	FCM	FCD
Age/gender	Young adults/ M=F	Young adults/ M=F	< 25 years/ M=F	Young adults/ M=F
Radiology	Cortical disruption, soft tissue extension	No damage to cortex, no invasion	Cortical disruption, soft tissue extension	No damage to cortex, no invasion
histology	Hypercellular stroma with some atypia and mitosis; no growth-plate cartilage; permeative growth pattern	Hypocellular stroma with rare atypia and mitosis; curvilinear trabeculae bone; focal hyaline cartilage	Hypercellular stroma with occasional atypia or mitosis; growth-plate cartilage; little collagen	Hypercellular stroma with rare atypia and mitosis; extensive islands of hyaline cartilage; prominent collagen

DISCUSSION

Since the first description of LGCO, multiple case reports and several case series have shown the initial diagnosis to be challenging due to its relatively nonspecific radiological and histological findings.[1,2] In a study by Malhas et al,[2] almost 40% (7 of 18) of LGCO diagnoses were made only after tumor recurrence although the initial diagnosis was benign. As in our case, many of the other patients in the series required multiple biopsies before a final diagnosis of LGCO was rendered.[2] LGCO is generally distinguished from benign tumors by its infiltrative growth pattern and immunohistochemistry or in situ hybridization of MDM2 or CDK4.[1,2,14,15] The most common diagnostic mimickers of LGCO are summarized in **Table 1**.

Due to striking radiologic and histologic similarities with LGCO, FCM can be a challenging differential as demonstrated by our case. Histologically, there are three defining features of FCM: a variably cellular fibroblastic proliferation without significant cytological atypia or mitotic activity, a characteristic cartilaginous component resembling an epiphyseal growth plate, and endochondral bone formation.[7,11-13] The cartilaginous component exhibits columnar hypertrophied chondrocytes and cartilage calcification with osteoblast rimmed lamellar bone formation.[11,18] The radiological and histological differential diagnosis for FCM includes benign lesions such as aneurysmal bone cyst (ABC), FD, and FCD, as well as malignant lesions such as fibrosarcoma, dedifferentiated chondrosarcoma (DDCS), and LGCO.[10,18-20] While FCM and LGCO have overlapping radiologic and histologic features, the distinguishing cartilaginous component of FCM is generally absent in LGCO.[2,6,21]

In our case, the presences of cellular islands of hyaline cartilage on the biopsies, along with more aggressive radiologic features, lead to the biopsy diagnosis of FCM. Although the resection specimen was sampled extensively, it did not demonstrate the characteristic cartilaginous component of FCM as shown in the biopsies. Taking into account the overall radiology and morphological features of the tumor, the cartilaginous element present in the biopsies fit into the morphologic spectrum of LGCO and the final diagnosis was eventually made. It is likely that the absence of characteristic cartilaginous features in the resection specimen is due to a paucity of that component in the original lesion and complete excision by the previous surgical procedures. In addition, the lack of *CPM* amplification in our case suggests that the LGCO may have more overlapping morphologic features with FCM than anticipated. More studies are needed to determine if there is any correlation between morphology and CPM amplification in LGCO.

Other differential diagnostic considerations of LGCO include FD and FCD. FD is the most common initial misdiagnosis in LGCO cases. FD is a non-neoplastic lesion with benign radiographic features (no cortical damage or soft tissue extension) composed of curvilinear trabeculae of metaplastic woven bone in a hypocellular fibroblastic stroma with only rare mitoses or atypia.[9,13,20,22] FCD is histologically very similar to FCM but with a benign radiologic picture and a more prominent collagenous component. Less common look-alikes include benign and malignant bone lesions such as nonossifying fibroma, ABC, well-differentiated fibrosarcoma, and parosteal sarcoma. In general, all these entities have significant radiologic and histologic overlap with LGCO.

CONCLUSION

The most challenging aspect of LGCO is initial diagnosis on limited tissue samples, and overlap of radiologic and histologic features with other osteolytic lesions. Our case emphasizes the importance of broad tumor sampling, molecular studies, and correlation of histology with radiology to arrive at the correct diagnosis.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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